REMARKS

Claims 1-24 remain in this application. Claims 1 and 13 are currently being amended. These amendments to the claims have been made to further prosecution. No new matter has been added.

Support for the amendments to claim 1 and claim 13 can be found in the application as filed on pages 10-18 and Tables 1-6. In particular, Table 5 shows a decrease in mean T cell numbers at 90 days at the higher 2-chlorodeoxyadenosine (2-CdA) dose (Group 3, N=3), with a decrease in both CD4+ T cells and CD8+ T cells. Table 6 presents the results of t-Tests, indicating a significant decrease compared to control (N=13) in mean T cell numbers at 90 days at the higher 2-chlorodeoxyadenosine dose ($P < 0.05$), with a decrease in both CD4+ T cells ($P < 0.05$) and CD8+ T cells ($P=0.06$).

Claim Rejections

Claims 1-24 stand rejected under 35 USC § 103(a) as being unpatentable over Nawrocki et al. (*Transplantation Proceedings*, 28: 3538-3539, 1996) taken with Cramer et al. (*Transplantation Proceedings*, 29: 616, 1997) and Schmid et al. (*Eur. Surg. Res.*, 30: 61-68, 1998). Copies of the documents discussed below that are not already of record are provided in the accompanying Supplemental Information Disclosure, and are referred to herein by the reference code used in the accompanying USPTO Form 1449.

The Claimed Invention

The Office Action dated January 24, 2005 stated that "the determination of chronic allograft rejection by histological examination would not change the outcome of the methods." The Applicant respectfully submits that the limitation of the presently amended claims "wherein the administration produces a decrease in cell-mediated immune responses including decreased levels of CD8+ T cells in the peripheral circulation," would have an effect on the methods, in requiring a reduction of a class of T-cells reported to be involved with the basic vascular pathology of chronic allograft rejection.

Immunophenotypic analyses have shown that the arterial inflammation characteristic of chronic allograft rejection consists primarily of an admixture of T cells and macrophages, and in some studies, CD8+ T cells are the most common, a subset of which show perforin positivity, thus identifying a cytolytic effector pathway. *See* Demetris, et al., *Pathophysiology of Chronic Allograft Rejection CME*, March 29, 2000, http://www.medscape.com/viewprogram/336_pnt, visited 7/21/2005, page 12 (citations are to the pages of the attached hardcopy submitted with the accompanying Supplemental Information Disclosure as document BF). Perforin has been shown to play a primary role in T cell-induced endothelial injury of the graft vascular disease of chronic rejection (Choy, J.C., et al., Perforin mediates endothelial cell death and resultant transplant vascular disease in cardiac allografts, *Amer. J. Pathol.*, 165: 127-133, 2004, copy submitted with the accompanying Supplemental Information Disclosure as document BE). CD8+ T cells have been shown in several animal models to contribute significantly to chronic rejection. Fishbein, M.P., et al., Role of CD8+ lymphocytes in chronic rejection of transplanted hearts, *J. Thoracic Cardiovasc. Surg.* 123: 803-809, 2002 (submitted with the accompanying Supplemental Information Disclosure as document BG). The authors of the latter study made the suggestion that the control of chronic rejection requires interventions directed to CD8+ lymphocytes. Id.

The claimed invention is directed to a method of ameliorating chronic allograft rejection in a human or animal allograft recipient comprising administering to the recipient in need of such treatment, in combination, a therapeutically effective amount of cyclosporin (CsA) at least once weekly and a therapeutically effective amount of 2-chlorodeoxyadenosine at least once weekly, wherein the administration results in a decrease in cell-mediated immune responses including decreased numbers of CD8+ T cells in the peripheral circulation (claim 1, currently amended). In another embodiment, the claimed invention is directed to a method of preventing chronic allograft rejection in an allograft recipient comprising administering to an allograft recipient a therapeutically effective amount of cyclosporin at least once weekly and a therapeutically effective amount of 2-chlorodeoxyadenosine at least once weekly, wherein the administration results in a decrease in cell-mediated immune responses including decreased numbers of CD8+ T cells in the peripheral circulation (claim 13, currently amended).

None of the cited references discloses or suggests the administration of a therapeutically effective amount of cyclosporin in combination a therapeutically effective amount of 2-

chlorodeoxyadenosine to produce a decrease in cell-mediated immune responses including decreased numbers of CD8+ T cells in the peripheral circulation. Therefore, the cited references, alone or in combination, do not disclose or suggest the present claimed invention, and the rejection of claims 1-24 under 35 USC § 103(a) is unwarranted. The Applicant respectfully requests that the rejection be withdrawn and the claims proceed to issue.

The Cited Prior Art

The previous Office Action characterized the Nawrocki et al. reference as disclosing a method wherein "said composition is administered subcutaneously and is efficient to suppress the recipient's B-cell mediated response to the allograft". See Office Action of June 28, 2004 at 3. The Nawrocki et al. reference is further characterized as teaching a combination "resulting in efficient inhibition of B-cell function including activation, differentiation, and immunoglobulin production". Id. at 5-6. Thus, with respect to the presently amended claims, Nawrocki et al. does not teach a composition that results in a decrease in cell mediated immune responses and, moreover, is silent as to the effect on CD8+ T cells. Further, Nawrocki et al. teach away from the present claimed invention to the extent it emphasizes an effect on B-cell function.

The Cramer et al. reference is also silent as any effect or role of CD8+ T-cells. The combination of the Cramer et al. reference with the Nawrocki et al. reference does not cure the defects of the Nawrocki et al. reference. The Schmid et al. reference does not report results of treatment on B-cells or T-cells in general or CD4+ or CD8+ T cells in particular. Thus, the combination of the Schmid et al. reference with the Nawrocki et al. reference and the Cramer et al. reference does not teach or suggest the present claimed invention.

The Schmid et al. cited reference is an extension of a study on the treatment of acute rejection in small bowel transplantation (Oberhuber, G., et al., Evidence that 2-chlorodeoxyadenosine in combination with cyclosporine prevents rejection after allogeneic small bowel transplantation, *Transplantation 58(6)*:743-5, 1994; submitted with the accompanying Supplemental Information Disclosure as document BP). The Oberhuber et al. publication and the Schmid et al. reference share three authors (Thomas Schmid and senior authors Raimund Margreiter and Günther Konwalinka) and a common protocol: the study concluded on day 10 post-transplantation. The authors distinguish their study in the acute phase of rejection from a

study of chronic rejection, and state that it is necessary to find out whether the treatment regimen using a combination of cyclosporin and 2-chlorodeoxyadenosine would be effective in preventing chronic rejection.

> In conclusion, we suggest that combining low-dose 2-CdA (0.1 mg/kg b.w.) with low-dose CsA (1.0 mg/kg b.w.) is highly effective in preventing acute rejection after allogeneic small bowel transplantation in rats. Complete abrogation of rejection in four of the five animals, as proven histologically, encourages further studies. It must be considered, however, that these experiments deal with rejection episodes occurring in the early postoperative period. To improve posttranplantation maintenance therapy it is necessary to find out whether this new regimen proves effective in preventing chronic rejection, which is still considered a major problem in clinical transplantation. Oberhuber et al., p 744.

Since the Oberhuber et al. publication refuses to extend the results of a study of the treatment of acute rejection ending at 10 days to speculate on the possible effectiveness of such treatment on chronic rejection, it is clear that the reference teaches away from concluding that a treatment effective for acute rejection would be useful for ameliorating or treating chronic allograft rejection without further studies on chronic allograft rejection. The statement that it would be obvious to one of ordinary skill is unsupported, if not contradicted, by this scientific publication by researchers in the field who are co-authors of one of the cited references. The cited Schmid et al. reference, alone or in combination with the cited Cramer and Nowracki references, does not render the claimed invention obvious under section 103(a).

The cited references that disclose the use of cyclosporin and 2-CdA in combination focus on the problem of acute allograft rejection. This focus is highlighted in the introduction (first paragraph) of the Nawrocki et al. article which states "Graft rejection has been the main problem in transplantation since the beginning. This reaction is due to differences in histocompatibility antigens between the donor and organ recipient". In fact, review articles, written at the time the invention was made discuss the etiology and pathology of chronic graft rejection and emphasize: "there is still no treatment to inhibit or prevent CTD [chronic transplant dysfunction], and a conclusive therapeutic strategy is not within hand's reach since its etiology and patho-physiology are poorly known". Kouwenhoven et al., Etiology and pathophysiology of chronic transplant dysfunction, *Transplant Int.* 13:385-401, 387 (2000) at 386: submitted with the accompanying Supplemental Information Disclosure as document BN. See also: Demetris, et al., 2000

document BF; Knoop C, et al., Immunosuppressive therapy after human lung transplantation, Eur Respir J. 2004 Jan;23(1):159-71, document BL.

The Rejection Under 35 USC §103(a).

The case law addressing the requirements for establishing a *prima facie* 35 USC § 103(a) rejection is well settled. In particular, establishing a *prima facie* case of obviousness under 35 USC § 103(a) requires that each of three requirements must be met. First, the references, taken alone or in combination, must teach or suggest each and every element recited in the claims. See M.P.E.P. § 2143.03 (8th ed. Rev. 1, Feb. 2003) citing In re Royka, 490 F. 2d 981, 180 USPQ 580 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references in a manner resulting in the claimed invention. And third, a reasonable expectation of success must exist. Furthermore, each of these requirements must "be found in the prior art, and not be based on applicant's disclosure." M.P.E.P. § 2143 (8th ed. Rev. 1, Feb. 2001). Determinations of *prima facie* obviousness must be supported by a finding of "substantial evidence." *See* In re Zurko, 258 F. 3d 1379, 1386 (Fed. Cir. 2001). Specifically, unless "substantial evidence" is found in the record that supports the factual determinations central to the issue of patentability, including motivation, the rejection is improper and should be withdrawn. Substantial evidence is something less than the weight of the evidence but more than a mere scintilla of evidence. In re Kotzab, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313 (Fed. Cir. 2000). In this case, there is no "substantial evidence" in the record to support the combinations alleged by the Examiner, nor is there the requisite "clear and particular" motivation required to support a *prima facie* case of obviousness.

The Patent and Trademark Office has the burden under section 103 to establish a *prima facie* case of obviousness. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q2d 1596 (Fed. Cir. 1988). It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. Id. Until the Office has met the burden to establish a *prima facie* case of obviousness, the burden of rebutting that case does not shift to the Applicant.

The Applicant respectfully submits that the Patent and Trademark Office has not borne the burden to establish a *prima facie* case of obviousness, and requests that all rejections under 35 USC § 103 (a) be withdrawn.

At best, the Office Action is advancing an "obvious to try" argument. "An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." In re Eli Lily & Co., 902 F.2d, 943, 945 (Fed Cir. 1990). However, "obvious to try is not the standard," what is required is a "reasonable expectation of success". In re O'Farrell, 853 F.2d 894, 904, (Fed. Cir.1988). The etiology and the pathology of chronic transplant dysfunction was and is conceded to be extremely complex and poorly understood. Moreover, the treatment modalities advocated, at the time the invention was made, to treat chronic graft rejection or chronic transplant dysfunction not only do not include use of 2-CdA in conjunction with cyclosporin but actually include eliminating cyclosporin to inhibit transplant toxicity. See Demetris, et al., document BF, pages 31-34; Kobashigawa J., What is the optimal prophylaxis for treatment of cardiac allograft vasculopathy? Curr Control Trials Cardiovasc Med. 2000;1(3):166-171, document BK.

The Office relies on In re Best for the proposition that "obviousness is not the express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest". However, In re Best, is an inapposite for several reasons. First, none of the cited references suggest, collectively or individually, administering an effective combination of cyclosporin and 2-CdA to treat chronic allograft rejection wherein the administration produces a decrease in cell-mediated immune responses including decreased levels of CD8+ T cells in the peripheral circulation. Second, In re Best was decided on the basis of a claimed cool-down step, which was found to be inherent in the prior art. In contrast, the present invention, recited in the amended claims, includes elements that are absent in the prior art, an effect on the cellular immune response, specifically decreasing the levels of circulating CD8+ T-cells, and are completely absent in the cited references.

Claims 1-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Nawrocki et al. taken with Cramer et al. and Schmid et al. For the reasons discussed above, the Applicant believes that this rejection is moot in view of the present amendments; withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the amendments and arguments presented herein, the Applicant respectfully request reconsideration and a timely Notice of Allowance to follow in this case. The Applicant requests that the Examiner telephone the undersigned at 608-284-2621 in the event a telephone discussion would be helpful in advancing the prosecution of the present case. The Commissioner is authorized to charge any additional fees or underpayment of fees regarding this response, including extensions for reply and Supplemental Information Disclosure Statement, to Deposit Account 07-1509.

Respectfully submitted,

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